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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/596,348	07/14/2006	Thomas Ivo Cremers	484-US-PCT	5528

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EXAMINER	
RAO, SAVITHA M	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
11/17/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/596,348	CREMERS ET AL.	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *13 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-21,35 and 36* is/are pending in the application.

4a) Of the above claim(s) *5-11 and 18--21 and 35-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 12-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 5-21 and 35-36 are pending.

Receipt and consideration of Applicants' amended claim set, declaration and arguments filed on 08/13/2009 is acknowledged. Claims 2-4, 22-34 and 37-42 were cancelled. Claims 5-11, 18-21 and 35-36 are withdrawn from consideration as being drawn towards a nonelected invention.

Claims 1 and 12-17 are under consideration in the instant office action.

Applicants' arguments, filed 08/13/2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Rejection of Claims 1 and 12-17 under 35 U.S.C. 103(a) as being unpatentable over Tollefson et al (EP 0966967, referenced in the instant IDS) in view of Morisset et al (The Journal of Pharmacology and Experimental therapeutics, Vol 288 (2), 1999, 590-596, referenced in the instant IDS), Leurs et al (TIPS, May 1998, Vol (19) 177-183 and Schlicker et al (European Neuropsycopharmacology, Vol 10, supplement 3, Sept 2000, pages 199-200) is maintained for reasons of record reiterated below.

Tollefson et al teaches methods and compositions for the treatment of Bipolar disorder, Bipolar depression or unipolar depression by employing a compound having an atypical antipsychotic effect and a serotonin reuptake inhibitor (abstract). The first compound is an atypical antipsychotic such as clozapine, olanzapine, which are both

known compounds that are clinically effective in the treatment of schizophrenia [0011] and the second component is a serotonin reuptake inhibitor which among others include citalopram, which drug Tollefson teaches as a serotonin reuptake inhibitor and is clinically effective in depression ([0012], line 40-43). Tollefson teaches the combination of olanzapine/citalopram among the preferred combination [0018]. Tollefson teaches that the adjunctive combination may be administered as a single pharmaceutical compositions which may take any physical form which is pharmaceutically acceptable such as tablets [0038] and the inert ingredients and manner of formulation of the adjunctive pharmaceutical compositions are conventional [0039] for example capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the mixture in the capsules [0040] which reads on the pharmaceutically acceptable carrier limitation of instant claim 12.

Tollefson does not teach clozapine and olanzapine to have H3 receptor antagonistic properties.

However, Morisset et al teaches that clozapine and olanzapine behaves as weak H3 receptor antagonists in vitro with Ki around 1 and 50 μM respectively. Morisset teaches that despite the modest affinities displayed by both these compounds, the compounds nearly doubled steady-state tele-methyl histamine (t-MEHA) levels in brains with ED50 values comparable to those of potent H3-receptor antagonists (abstract). Morisset teaches that clozapine administration resulted in an enhancement of t-MEHA levels of about 100% i.e. in the same range as that elicited by H3-receptor antagonists such as thioperamide of ciproxifan (page 593, right col. 2nd paragraph).

Leurs teaches the therapeutic potential of histamine H3 receptor agonists and antagonists (title). Leurs teaches that in the mammalian brain, histamine-containing cell bodies are located in the tuberomammillary nucleus of the posterior hypothalamus and project to most cerebral areas indicating that H3 receptor ligands can potentially affect a variety of brain functions. Additionally H3 receptors are involved in the presynaptic regulation of the release of neurotransmitters such as acetylcholine, dopamine, 5-hydroxytryptamine (5-HT) etc. (page 177, left col. 1st paragraph to right col. 1st paragraph). Leurs teaches thioperamide as a prototypic H3 receptor antagonist which possesses nanomolar affinity for the H3 receptor and fairly good penetration into the brain. (page 178, left col. 2nd paragraph -right col. 1st paragraph). Leurs concludes that the CNS effects of the H_3 receptor antagonists make them interesting candidates for testing in several disorders of the CNS and the highly localized CNS distribution of the H_3 receptor suggests that limited peripheral side-effects will be seen after treatment with an H_3 receptor antagonist (page 182, right col. 3rd paragraph to page 183, left col. 1st paragraph).

Schlicker et al that histamine H3 receptor is a typical example of a presynaptic autoreceptor in that it is located presynaptically on the nerve endings of the histaminergic neurons in the CNS where its activation produces inhibition or histamine release. It is also located presynaptically on axon terminals of non-histaminergic neurons and thereby H3-receptor activation inhibits the release of serotonin, dopamine and noradrenalin in the CNS. (page S199, right col. S.24.02 column1). Schlicker additionally suggests that the blockade of H3 receptors is an accidental property of

already available drugs such as clozapine which is a moderately potent H-3 receptor antagonist (pKi 6.2) (page S200, left col. 2nd paragraph)

In view of the foregoing references, the instantly claimed pharmaceutical composition comprising one compound which is a serotonin reuptake inhibitor and a second compound which is a H3 receptor antagonist having an affinity for the H3 receptor below 0.5 μM would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made. Tollefson teaches pharmaceutical compositions comprising citalopram a serotonin reuptake inhibitor with clozapine and olanzapine. Morisset teaches clozapine and olanzapine to have weak H3 receptor antagonistic activity around 1-50 μM. Leers teaches thioperamide as a prototypic H3-receptor antagonist with nanomolar affinity for the H3 receptors and states that H3 receptors are involved in the presynaptic regulation of the release of neurotransmitters which include 5-HT (serotonin). Schlicker also teaches that H-3 receptor activation inhibits the release of serotonin, dopamine and noradrenalin in the CNS. As such the resulting action of both the H3-receptor antagonists and serotonin reuptake inhibitors (which inhibits the reuptake of serotonin into the presynaptic cells) would be to increase extracellular level of the neurotransmitter serotonin. It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. In re Kerkhoven, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. In re Crockett, 126 U.S.P.Q. 186, 188 (CCPA 1960). Accordingly, to establish obviousness

in such fact situations it is NOT necessary that the motivation come explicitly from the reference itself (although the Examiner believes it does, as discussed supra). The natural presumption that two individually known drugs which increases extracellular levels of serotonin and thereby help in treatment of depression would, when combined, provide a third composition also useful for treating depression flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (e.g. unexpected results) to rebut this natural presumption. Accordingly, an ordinarily skilled artisan would be motivated to combine the teachings of Tollefson, Morisset, Leurs and Schlicker to develop a composition comprising citalopram and thioperamide.

Since Tollefson has already demonstrated that a serotonin reuptake inhibitor such as citalopram can be combined in a composition with a weak H3 receptor antagonist such as clozapine for treating depression, Leurs provides additional motivation for one of ordinary skill in the art to utilize a stronger H3-receptor inhibitor such as thioperamide instead of clozapine/olanzapine in combination with citalopram in the composition of Tollefson specially for treatment of CNS disorders since there is an highly localized CNS distribution of H3-receptors which would suggest that limited peripheral side effects will be seen after treatment with and H3-receptor antagonist.. Accordingly an ordinarily skilled artisan will be imbued with at least a reasonable expectation of success that such a composition would provide good therapeutic results with decreased side effects.

Response to applicant's arguments filed on 06/01/2009

Applicant's arguments filed 6/01/2009 have been fully considered but they are not persuasive.

Applicant traverses the above rejection with the following arguments:

a. Tollefson et al. neither teaches nor implies that clozapine and olanzapine have H3 receptor antagonistic properties.

b. Morrisset et al. teaches that clozapine and olanzapine ore very weak H3 receptor antagonist with 1 and 50 μM Ki values respectively. Morisette teaches that clozapine and olanzapine induce tele-methyl histamine levels which are not relevant to the claimed invention which related to enhanced serotonin levels in the brain. Morisset makes no suggestion with regard to H3 activity having a role in anxiety, depression or other affective disorder.

c. Leurs does not mention disorders related to anxiety or depression. Leurs et al descirbes that H3 receptors inhibit the release of 5-HT in rat hypothalamus and teaches away from the claimed invention. Leurs concludes that

d. Schlicker describes that the effect of H3 receptor antagonist on monamine release is not so very likely.

e. Applicant submit declaration under 1.132 showing unexpected results obtained with the combination of thioperamide/ciproxafan (high affinity H3 receptor antagonists) with Citalopram (a serotonin reuptake inhibitor).

Applicant's traversal arguments for this rejection have been fully considered, but are not found to be persuasive.

In response to applicant's arguments against each reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this instance, while Tollefson describes compositions for the treatment for bipolar disorder and depression comprising combination of clozapine or olanzapine and a serotonin reuptake inhibitor, Morisset teaches clozapine and olanzapine to have weak H3 receptor antagonistic activity around 1-50 μM. Leers teaches thioperamide as a prototypic H3-receptor antagonist with nanomolar affinity for the H3 receptors and states that H3 receptors are involved in the presynaptic regulation of the release of neurotransmitters which include 5-HT (serotonin). Schlicker also teaches that H-3 receptor activation inhibits the release of serotonin, dopamine and noradrenalin in the CNS. As such the resulting action of both the H3-receptor antagonists and serotonin reuptake inhibitors (which inhibits the reuptake of serotonin into the presynaptic cells) would be to increase extracellular level of the neurotransmitter serotonin. As such applicant is again reminded that it is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. In re Kerkhoven, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. In re Crockett, 126 U.S.P.Q. 186, 188 (CCPA 1960).

In response to the arguments against Tollefson, even thought Tollefson does not teach the H3 receptor antagonistic activity of clozapine and olanzapine, the receptor antagonistic property of the compound is an inherent feature and characteristic of those compounds. It is also noted that "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). As such the instantly claimed H3 receptor antagonistic property of olanzapine and clozapine would be present in the same compounds taught by Tollefson in combination with serotonin reuptake inhibitor.

In response to applicant's arguments against Morrisset, this reference is included in the rejection above for its teaching that clozapine and olanzapine are indeed H3 receptor antagonists albeit not the high affinity ones. Combination of the teachings of Morrisset and Tollefson would provide an ordinarily skilled artisan to develop compositions comprising an H3 receptor antagonist with a serotonin reuptake inhibitor. In response to applicant's argument that the Morrisset fails to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that clozapine and olanzapine induce tele-methyl histamine levels which are not relevant to the claimed invention which is related to enhanced serotonin levels in the brain) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicants arguments that Morisset and Leurs makes no suggestion with regard to H3 activity having a role in anxiety, depression or other affective disorder, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. As such the properties of clozapine, olanzapine and thioperamide to inhibit H3 receptors would result in the intended result of having a role in anxiety, depression and other affective disorders.

In response to applicants arguments that Schlicker et al teaches that the possibility that effects of the H3 receptor antagonists on the release of serotonin, dopamine and noradrenaline contribute to the behavioral responses is not so very likely, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). It is also noted that "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." In re Heck, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting In re Lemelson, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)). A reference may be relied upon for all that it would have reasonably

suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). In this instance, Schlicker also suggests the involvement of H3 receptor antagonists having favorable effects on learning and memory in rodents and protection against seizures in a rat model of epilepsy (Abstract S.24.02 second paragraph).

With regards to the Applicant's argument of unexpected results, Applicants data presented in the 1.132 declaration and the instant disclosure as cited in the response of 08/31/2009 has been considered and found to be unpersuasive. Applicants have demonstrated the effects of co-administration of thioperamide or ciproxifan both of which are high affinity H3 receptor antagonists with citalopram, a serotonin reuptake inhibitor which results in a synergistic increase in the 5-HT levels. Applicants have however, not shown the same experiment with a low affinity H3 receptor antagonists. Absence of evidence to the contrary, the low affinity H3 receptor antagonists such as olanzapine/clozapine could very well elicit synergistic increase in 5-HT levels when co-administered with citalopram. Applicant's present no data to show otherwise. Additionally, while the data presented provides support for the combination of Citalopram with Ciproxifan and a combination of Citalopram and Thioperamide, it does not provide support for the combination of all the different serotonin reuptake inhibitors sited in instant claim 16 and all the H3 receptor antagonists cited in instant claim 17. Further the experiments in the instant declaration and disclosure were conducted with very specific concentrations of the said drugs for

e.g. citalopram was used at 10 µmol/kg, thioperamide was used at 12.25 µmol/kg and ciproxifan at 1 and 15 mg/kg. In addition, the route of administration for all these three agents was subcutaneous. Absence of evidence to contrary, the exact concentration of the agents and the route of administration used may be critical to achieve the synergistic effect observed in the study. The instant claims do not recite these limitations required to achieve synergistic effect. For example, instant claim is drawn to a pharmaceutical composition comprising one compound which is a serotonin inhibitor and a second compound which is a high affinity receptor antagonist. Therefore, the unexpected results observed in these studies are with very specific parameters and specific compounds and are therefore not commensurate with the full scope of what is claimed and the data is not probative of nonobviousness of the full scope of the claims as discussed above.

Accordingly, the arguments set forth by the applicant are unpersuasive and the rejection is maintained.

Conclusion

Claims 1 and 12-17 are rejected. No claims are allowed

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614